REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-10 and 15-24 are pending. Claims 11-14 drawn to nonelected subject matter have been canceled without prejudice or disclaimer to their later prosecution in another application and to allow the addition of new claims 21-24.

Claims 1-10 and 15-20 were rejected under Section 112, first paragraph, on pages 2-9 of the Action because it was alleged that "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims." Applicant traverses for the following reasons.

Applicant submits that new claims 21-24 are fully consistent with the Examiner's finding of enablement. As regards the other claims, Applicant submits that they satisfy the requirement for limiting the claimed invention to detection of homozygous loss of both wild-type *POLG* 10-repeat alleles or detection of compound heterozygous *POLG* mutant alleles (i.e., one *POLG* mutation with a length variant other than 10 repeats and another pathological *POLG* mutation) but that the skilled artisan is not limited to gene-technological methods (i.e., a RNA- or DNA-based molecular genetic technique like RT-PCR or PCR, respectively) for detecting *POLG* mutations. Protein-based methods can distinguish the loss or gain of CAG microsatellite repeats by a change in molecular weight. Other pathological mutations in the coding region of *POLG* can be detected by changes of charge or antigenicity.

A large database of *POLG* mutations and polymorphisms exists and is available to the public, arising from studies of the role of this gene in autosomally determined progressive external ophthalmoplegia (adPEO). Over 20 pathological mutations in other parts of the gene are now known (e.g., see Van Goethem et al., Neuromuscul. Disord. 13:133-142, 2003; Agostino et al., Neurology 60:1354-1356, 2003), and can clearly be distinguished from polymorphisms which do not cause pathology (see, e.g., the *POLG* database at www.genome.utah.edu/genesnps/cgi-bin/frame.cgi?gene_id=345). A database of pathological mutations in *POLG* is maintained by Dr. W.C. Copeland (NIEHS) and will shortly be released into the public domain as a continuously updated, curated

website. Gene sequencing of RNA or DNA samples from male patients with only one CAG microsatellite-repeat length other than 10 repeats can unambiguously assign them as compound heterozygotes (or not) without any need for prophecy.

Since many different alleles of *POLG* are already identified in cases of recessive adPEO, and are thus, by definition, loss of function or null alleles, an individual that is a compound heterozygote for a CAG microsatellite-repeat length variant and one of these alleles will be functionally equivalent to an individual with two mutant alleles at the CAG microsatellite repeats (i.e., lacking wild-type function). While the molecular mechanism by which CAG microsatellite-repeat length variants cause male infertility is unknown, this does not prevent use of the invention for rigorous genetic testing and screening. The invention does not require that a clinician understand such mechanisms; instead the clinician or geneticist uses the invention to diagnose a male patient as someone who is suffering from the disorder (e.g., claims 1 and 23) or has a genetic predisposition to suffer from the disorder (e.g., claims 2 and 24). This is consistent with the supporting data provided in the specification, and is incontestable from the data which is now available in the public domain and is referred to above.

Sequencing to reveal a second mutant allele does not require any such trial and error. The skilled artisan simply has to refer to the published data on *POLG* mutant alleles found in cases of recessive disease, such as R3P, A467T and so on. This is straightforward, immediate, and the conclusions are clear cut. An individual with two mutant CAG microsatellite-repeat length alleles (i.e., no wild-type 10-repeat allele) definitely has *POLG*-type male infertility. An individual who has one mutant repeat CAG microsatellite-repeat length allele as well as a pathological mutation in the other *POLG* allele elsewhere in the coding region of the gene also suffers from POLG-type infertility. An individual who has one mutant CAG microsatellite-repeat length allele, but only harmless polymorphisms or no other sequence variants at all in the other allele, does not suffer from *POLG*-type infertility. There is no element of prophecy or unpredictability. The data provided in the specification supports the claimed invention and enables the skilled artisan to make a diagnosis or screen for genetic predisposition without undue experimentation.

Withdrawal of the enablement rejection made under Section 112, first paragraph, is requested because it would not require undue experimentation for a person of skill in the art to make and use the claimed invention.

Having fully responded to all of the pending objections and rejections contained in the Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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